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Anticoagulant Drug Treatment of Coronary Artery Disease

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• **Anticoagulant therapy of arteriosclerotic heart disease may prove to be most valuable when applied on a long-term basis for prevention of recurrent myocardial infarction. While its prophylactic value in impending infarction has not been established, at least the accepted treatment for the acute stage is already begun if an anticoagulant has been administered before an inevitable infarction occurs.**

The chief value of the anticoagulant, though, seems to lie in preventing cardiac mural thrombosis and extracardiac thromboembolism. It is by this effect, apparently, that mortality has been reduced by 50 per cent among survivors of myocardial infarction who receive continuous dicoumarin therapy.

While the danger of hemorrhage is still present, it is being steadily reduced by increasing skill in the management of anticoagulant therapy, and for a long time the risk has been far outweighed by the reduction in coronary occlusion.

Physicians have a duty to learn the use of anticoagulant therapy, obtain the facilities necessary for it, and apply it to patients who are able and willing to cooperate in prolonging their useful lives.

ARTERIOSCLEROTIC HEART DISEASE causes over 400,000 deaths annually in the United States,[27] and most of these deaths are due to thrombotic coronary artery occlusion. The ideal treatment is largely a problem of preventive medicine. Hand in hand with measures for the prevention of the primary atherosclerosis must go those for the prevention of secondary thromboembolic complications. The question of possible salvage from antithrombotic drug therapy for prevention of death in myocardial infarction is highly debatable. In 1954 the Committee on Anticoagulants of the American Heart Association concluded from a study of 1,031 cases that the death rate could be reduced by one-third.[28] There are those, however, who still reject the drugs outright; others who would use them only in acute infarction for what they consider "bad risk" cases; and there is the same committee's opinion that anticoagulants should be given prophylactically for three to four weeks in all cases unless contraindicated by a risk of severe bleeding. Still more dubious is the status of long-term anticoagulant drug therapy for preventing a recurrence of myocardial infarction in survivors of the first attack. Some physicians never use long-term therapy, others wait for a second attack or other signs of thromboembolism, and others would use it in every case in which it is not contraindicated. These different interpretations arise from clinical and pathologic statistical studies that are necessarily imperfect. The chances for error in the random selection of patients, and for error and bias in observation, are too great for a perfectly controlled study. The only statistically

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perfect study of anticoagulant therapy would be by the double-blind placebo technique, and such a study is impracticable, especially in the evaluation of long-term therapy.[16]

Despite certain unavoidable technical flaws, the committee's study of 1,031 cases was the most comprehensive possible. Other reports which have disagreed are based on series that were either numerically too small or inadequately controlled. Shall we act on evidence which is only presumptive and not conclusive? Many crucial clinical decisions are based on just such evidence. As Samuel Butler said, the art of good living consists in the "ability to come to adequate conclusions from inadequate evidence." This applies equally well to the art of good medicine. Immanuel Kant put it more incisively: "Again and again it is necessary to take a decision on the basis of knowledge sufficient for action but insufficient to satisfy the intellect."

One might wish that the evidence for anticoagulant therapy were flawless enough to satisfy the intellect of all clinicians, but it is sufficient, I believe, for therapeutic action.

This discussion of the treatment will be limited largely to the coumarin derivatives. Heparin, although quicker and more potent, does not maintain an adequate anticoagulant effect longer than 16 to 18 hours without repeated injections. Therefore, its usefulness, except for the lipolytic effect, is limited to thromboembolic attacks and to the first few days of acute myocardial infarction. There are many questions that must be answered about antithrombotic therapy:

First: In patients with symptoms of impending myocardial infarction, can early treatment prevent the attack? Presumably this would occur through prevention of thrombosis. The results have been disappointing and certainly not convincing.[7,22,23]

Second: Can anticoagulant therapy prevent propagation of a coronary arterial thrombus that has already occluded a vessel? Theoretically it should, but the available evidence does not support the assumption.[5]

Third: Can it prevent cardiac mural thrombosis? In a number of studies analyzing necropsy data on patients who had had acute myocardial infarction it was concluded that mural thrombosis was prevented in about half the treated group.* The Committee on Anticoagulants noted, though, that "relatively few of the participating physicians gave doses the first three days sufficiently high to achieve optimal therapeutic levels by the fourth or fifth day of dicumarol therapy." This failure in early treatment apparently could account for the failure to prevent mural thrombi in a larger number of cases, and argues for the early administration of heparin as well as dicoumarin. As regards long-term therapy, Bjerkelund's necropsy study (the only adequate controlled necropsy study I could find), disclosed a left ventricular mural thrombus in only one of nineteen treated patients compared with six of twenty-four controls.[4]

Fourth: How is extracardiac thromboembolism affected? The clinical diagnosis of thromboembolism is notoriously inaccurate. The committee observed that venous thrombosis and embolism of the lungs, brain, abdomen and extremities seemed to be significantly reduced, and necropsy data accorded with this conclusion. Among untreated patients, emboli, with or without infarction, averaged 125 per 100 cases, as against 45 per 100 of the treated. The main antithrombotic effects in acute myocardial infarction, therefore, are in the prevention of cardiac mural thrombi and extracardiac thromboembolism.

Fifth: Can continuous dicoumarin therapy prevent recurrent coronary artery thrombosis and reduce mortality? Nichol and Fassett[18] first suggested that it might in 1947. All the long-term studies of survivors of acute myocardial infarction, ranging from two to ten years' observation, have shown a reduction in mortality among the treated group to half or less of the rate in the untreated group. Bjerkelund's study of 119 treated and 118 untreated patients, whom he kept under observation for three to three and a half years, is one of the most carefully controlled of the long-term studies, and is the only one in which necropsy data is available on both groups. He reported a reduction of 45 per cent in recurrent infarction and of 37 per cent in mortality from cardiovascular disease. At necropsy of 43 patients, coronary thrombosis was noted twice as frequently in the control group as in the treated. Suzman, Ruskin and Goldberg,[24] and Manchester[15] found a significant reduction in mortality from recurrent infarction in treated patients observed from four to ten years. Other studies, although not well controlled, have shown a considerably less than the statistically anticipated mortality for two to three years following the initiation of anticoagulant prophylaxis.[12,17,19,25]

Sixth: What are the risks of bleeding? First, it should be emphasized that a risk of serious bleeding is the only justifiable contraindication to anticoagulant therapy. A little bleeding ordinarily cannot kill; a little clotting can. Second, the risk of bleeding incurred by anticoagulant therapy cannot be judged except by comparison with a comparable control group. Third, the details of treatment must be considered. Reports of hemopericardium and other effects of bleeding incurred by overdosage are irrelevant to evaluation of a drug whose contraindications and method of administration are now fairly well delineated. Most reports on serious hemorrhagic

*References 8, 9, 11, 13, 28.

complications reveal such deficiencies of methods.† Intracardiac hemorrhage and rupture are the major hazards from anticoagulant therapy in acute myocardial infarction. In mild infarction this danger is negligible, and in a large series comprising both mild and severe cases it is still small. The committee estimated that in each 100 cases treated, anticoagulant therapy might be expected to cause two more deaths from rupture or hemorrhage than would be expected without this treatment. "This regrettable loss," the committee added, "fortunately is counterbalanced by a substantially lower expectation of death due to thromboembolism." In long-term therapy, the statistical incidence of moderate or severe bleeding has been about once every 13 to 20 years of treatment per patient. Serious episodes have been those of cerebral hemorrhage in patients with hypertension.

DISCUSSION

If one dismisses the radical view (which was expressed recently to me in a personal communication) that since anticoagulant drugs are used to kill rats, they should not be used in man, there are reasons behind the fairly clear-cut areas of agreement and disagreement that exist among clinicians. The available evidence receives varying interpretations as it passes through the thinking man's cerebral filter. Anticoagulant therapy is theoretically indicated in impending myocardial infarction even though its benefit in this situation is not measurable. Probably by the time the thrombotic milieu signals its presence with persistent angina, it is too late in most cases to prevent the impending occlusion, except by rendering the blood absolutely incoagulable. Moderate reduction of coagulability, however, may prevent coronary thrombosis in some cases. Moreover, it should diminish the size of the occluding thrombus and, in any case, if thrombosis occurs, the recommended therapy for the acute attack and for later prophylaxis is already initiated. Most observers who have had long experience with anticoagulants believe that in acute myocardial infarction, under proper conditions, the benefit of the drugs exceed the danger in the "good-risk" cases of low mortality, and even more so in severe cases. Burchell[6] sums up anticoagulant therapy in good-risk cases: "We are willing to give anticoagulant therapy to 100 or more patients with the hope of preventing one death." Long-term therapy, in the general opinion, is most beneficial for older patients with recurrent infarction or thromboembolism, but Bjerkelund[4] found the greatest benefits in patients under 60 years who had had only one infarct. The death rate in such patients was significantly reduced in the first year of observation. He suggested that the energy available for treatment would be most profitably expended on long-term therapy of relatively young patients who have had only one infarct.

†References 1, 2, 10, 14, 21, 26.

TREATMENT

For anticoagulant therapy there is no routine; but there is a method with clear-cut requirements. Success of the method depends, first, on the readiness and competence of the physician to apply it and, second, on the proper selection of the patient. Lack of experience and lack of immediate and reliable laboratory facilities are a definite contraindication which nevertheless can and should be overcome in many cases. Decision as to whether anticoagulants are indicated may be a perplexing one. In some communities and hospitals the majority of physicians, at least the more voluble ones, may so outspokenly oppose anticoagulant therapy in certain circumstances that the attending physician, unless strong in his own conviction, may be constrained to forego use of it. On the other hand (in a situation more frequently stressed) he may be urged toward this therapy by other physicians, by the patient or his relatives or (it is said) by the rather naive fear of being charged with negligence. In either situation he should consult, as he does in other clinical dilemmas, with a colleague also experienced in anticoagulant therapy.

The selection of the patient must not be based on any rough routine criteria, but rather on his specific need and, for long-term treatment, on his willingness and ability to cooperate. At times the indications and the contraindications may be of almost equal weight. Bay and co-workers[3] reported such an instance: A patient who had had several thrombotic coronary occlusions and intercurrently three massive hemorrhages from peptic ulcer, insisted on being given dicoumarin during recurrent thrombosis because he feared the danger of thrombosis more than that of hemorrage. It was decided to administer the drug as the lesser risk. Fortunately the need for such decisions is rare. In an acute case, if no consultant is at hand the attending physician's decision on the use of anticoagulant drugs is unassailable. If the danger of hemorrhage cannot be assessed for lack of laboratory service, or if it seems too great in the circumstances, a frank opinion can be given without fear of reprisal. Long-term anticoagulant therapy is the more demanding. The liaison between physician and patient becomes of paramount importance. Such therapy is not feasible in private practice unless a dedicated secretary and nurse are available, and they must have a bent toward amateur sleuthing in locating wayward patients. It is unwise unless the patient accepts equal responsibility in treatment.

The third consideration—given a competent physician with adequate facilities, given a clinical situation that justifies this therapy—the third consideration is the willingness and ability of the patient to cooperate, to come in for his blood tests, to report any significant experience, to follow the prescribed dosage and precautions and, above all, to keep in touch with the physician's office. Failure in this regard can nullify the benefit of treatment. The patient who at first seems cooperative may later fail in these requirements; and if he does, the physician had best gradually diminish dosage and then completely discontinue the treatment.

These, then, are the requirements for therapy. Are they enough? Will they protect the patient—and the physician—from the disquieting experience of sudden severe hemorrhage? My answer, and that of other physicians experienced with anticoagulant therapy, is yes, within the bounds of reasonable risk. First of all, bleeding is almost never spontaneous. As experience with hemophiliacs, and patients with a total loss of fibrinogen demonstrates, a person with virtually incoagulable blood does not bleed unless he incurs a vascular lesion.[20] Security, then, is in direct proportion to the thoroughness with which the physician seeks and rules out the causes of hemorrhage. Obviously it is impossible to detect, much less to evaluate, every potentially hemorrhagic lesion in the body. As the patient's prothrombin level is reduced, the risk of hemorrhage from such lesions increases. The next consideration, then, is to proportion the risk of hemorrhage to the risk of coronary thrombosis. No arbitrary prothrombin level can always protect against these opposing dangers. In acute myocardial infarction the danger of both cardiac thrombosis and cardiac hemorrhage is higher than in the chronic stage. In the latter, experience indicates that a fairly moderate prothrombin reduction gives good protection against thromboembolism without undue risk of hemorrhage.

The Committee on Anticoagulants believes that to receive the full benefits of anticoagulant therapy, the prothrombin content of the patient's blood should be kept, at all times, at a level indicated by at least 25 seconds for clotting (a value of 23 per cent or less). There is, however, the committee said, a definite but lesser therapeutic effect with a prothrombin time as short as 20 seconds (a value of 40 per cent). "A little anticoagulant protection," according to the committee, "is definitely better than none. In cases where excessive hemorrhage or other medical risk precludes the use of dicoumarin in the usual doses, or maintenance of the usual prothrombin levels, consideration should be given to the use of minimal doses such as would maintain the patient at about 20 seconds prothrombin time." Thus, even with a known cause of potential bleeding, a patient with severe myocardial infarction should not automatically be denied antithrombotic protection. On the other hand, a patient without a bleeding lesion need not be kept at a low prothrombin reduction for long-term treatment. In my experience, a prothrombin level of 40 per cent gives good protection against thrombosis, diminishes the risk of bleeding and permits an interval of several weeks between tests once a stable level has been determined. Until better means are available, then, anticoagulant drug therapy is here to stay. The problems ahead are to sharpen the criteria for patient selection, to improve the techniques in management, and to train more physicians in the method. It is the duty of medical schools now to give students a sound understanding of anticoagulant therapy and to present the areas of agreement and disagreement with an avoidance of bias. Equally, practicing physicians have a duty to become skilled in the technique and to be prepared to use it with confidence.

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